

139. A method according to claim 42, wherein said virus is administered at a site other than directly into a tumor of said cancer.

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REMARKS

The attached references are supplemental to the information previously filed and already considered by the examiner. Under 37 C.F.R. §1.97(d), an information disclosure statement filed after final action shall be considered by the Office if accompanied by a certification as specified in §1.97(e), a petition, and the petition fee. Such are attached herewith and accordingly consideration of the information is respectfully requested.

Entry of the amendment is respectfully requested. Support for the claims is clear from the record and the following exemplary disclosures, e.g., from parent application 08/055,519: tumor cytotoxicity of the virus, page 2, line 35 - page 3, line 2, Examples 1-3; direct cytolytic activity of the virus on cancer cells, page 5, lines 17-21, 33; freedom from tumor cells or components, Examples 1-3, compare disclosures identified on page 3, lines 3-9; freedom from red blood cells and membranes and effective steps of removal thereof, page 13, lines 31-34; systemic administration, page 7, line 20 and page 17, lines 33-35; tumor regression, page 4, lines 5-26; radiotherapeutic or chemotherapeutic agents, page 8, line 5; virus is attenuated, page 18, line 5; amount of NDV is at least  $10^7$ , page 15, line 1; biological agents, page 8, lines 1-35; without toxic sequelae, page 3, line 35; virus is genetically-engineered, '536, page 4, line 5; further comprising an agent possessing anti-cancer, immune-enhancing, of virus-enhancing activity, page 8, lines 20-23.

The foregoing amendments eliminate the ambiguity in the claims noted by the Examiner. For example, original independent claim 13 has been clarified to recite that the Newcastle Disease Virus is administered "in an amount which alone is cytolytic or cytotoxic" to the cancer being treated. Such amendment is in accordance with the examiner's suggestion on page 4 of the Office Action dated October 18, 1995. Claims

37-41 recite similar language. Each of claims 13 and 37-41 also recite at least one other feature clarifying the intended meaning of the claims, e.g., systemic administration, multiple doses, administration at a site other than directly into a tumor, exclusion of certain virus strains, substantial freedom from red blood cell membranes, subjected to low speed centrifugation. Since these claims also achieve the results achieved by the clarification suggested by the Examiner, it can be seen that no further searching is required. As for the dependent claims, these merely reflect alternate phraseology for defining the invention based on different combinations of the features discussed above, e.g., use of mesogenic strains, substantial freedom from red blood cells, or treatment by low speed centrifugation. The modifier "substantially free of" has its normal meaning in context, e.g., nothing more than the expected amount is remaining after positive efforts have been made to avoid addition of red blood cells or to remove red blood cells.

As recognized by the examiner, the various claims are patentable over the prior art in various ways, e.g., in the prior art amounts of NDV are not disclosed or are functionally unspecified; amounts are not cytolytic or cytotoxic alone, as in immunotherapy, requiring presence of tumor cell or tumor cell components; methods and/or experiments are not enabled or reproducible, such as, do not identify NDV strain, amounts, etc., or are anecdotal or taught as merely "worthy of more extensive evaluation", or were abandoned eventually by the authors (e.g., Csاتary, Cassel et al., Bohle, Schirrmacher); no tumor regression or only temporary regression described; do not employ lytic and/or mesogenic NDV strains or formulations which are substantially free of red cells, or the corresponding reference does not have an enabling disclosure from which such is determinable; treatment of mouse tumor in mouse host; etc.

In the Office Action dated January 4, 1995, claims 1-12 were rejected under § 103 as unpatentable over Reichard et al., *J. Surgical Res.* 52:448-453 (1992). As stated in the previous response of June 30, 1995, this publication reports research which is the work of the inventors of the subject matter of the present application. Consequently, it has been removed as effective prior art. It was also noted in the Office Action that the Reichard et al. paper was presented at the Annual Meeting of the Association for Academic Surgery in November 1991. The oral presentation at that meeting is similarly not prior art. A written abstract of the meeting presentation, however, was available at

least by November 1991. This abstract was provided to the P.T.O. in the Information Disclosure Statement (reference A56) submitted prior to the Office Action and discussed on page 16 of the response.

The provisional obvious-type double patenting rejection is moot since the parent is abandoned.

Rejection under § 112, first paragraph

Claims 23, 26, and 35 are rejected under § 112, first paragraph, allegedly for failing to provide support for the invention as it is now claimed.

Retinoic acid is disclosed on page 5, lines 28-30 of '519, and page 12, lines 6-10 of the present application, e.g., as enhancing the cytolytic effect of NDV. Retinoid acid is mentioned on page 8, line 31 of '519 and page 14, line 22 of this application.

In regard to the objection to the term "mesogenic", the subject matter of a claim need not be described literally for the specification to satisfy the written description requirement. It is sufficient that the specification reasonably conveys to those skilled in the art, to whom it is addressed, that the inventors had possession of the subject matter which is later claimed. In re Wertheim, 191 U.S.P.Q. 90 (C.C.P.A. 1976); Vas-Cath Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). Thus, a specification can support an embodiment even though a specific term used to describe it not expressly stated anywhere within a disclosure. It is sufficient if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an applicant had possession of the concept of what is claimed. Note, especially Kennecott v. Kyocera, 5 U.S.P.Q.2d, 1194 (Fed. Cir. 1987), where the Court (in the portion of the opinion unaffected by Vas-Cath) found written descriptions for an unmentioned crystal structure type based, *inter alia*, on the fact that the examples inherently had such structure type.

Attached is a declaration by Dr. Conrad Heilman, a skilled worker in the field, attesting to the fact that, upon reading the specification and its parent, a skilled worker would inevitably recognize the concept of administering a mesogenic strain of Newcastle Disease Virus to treat or detect cancer. (In re Alton, Case No. 94-1495 (Fed. Cir. 1996)) Dr. Heilman states that Newcastle Disease Virus is conventionally classified into three general categories: lentogenic, mesogenic, and velogenic. Upon reading the disclo-

sure (e.g., '519, Page 3, lines 10-20 and this patent, page 11, lines 5-12) that all Newcastle Disease Virus strains can be used according to the present invention, the skilled worker would have inevitably recognized that each of the three well-known categories of NDV, i.e., lentogenic, mesogenic, and velogenic NDV, the literal equivalents of the NDV genus, could therefore be used accordingly. That none of these categories is literally recited in the specification is immaterial since such classes are inherently embodied by the term Newcastle Disease Virus. Furthermore, a mesogenic strain, MK107, is actually exemplified in the specification. Dr. Heilman states that a skilled worker would have immediately recognized that inherently MK107 is a mesogenic strain. Such disclosure, he attests, coupled with the express generic statements that Newcastle Disease Virus is useful according to the present invention, clearly describes to the skilled worker at least the concept of administering a mesogenic strain of NDV to treat or detect cancer.

#### Rejection under § 102

Claims 13-18 and 20 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Bohle et al., Cassel et al., and Murray et al.

As discussed above, the classified versions of the claims adopt the Examiner's implied suggestions and thus under this rejection are moot.

In the mentioned publications, an oncolysate or vaccine prepared from Newcastle disease virus and tumor cells is administered intra- or subcutaneously as an immunostimulant to augment the immune response against antigens present on cancer cells. See, e.g., Murray et al., Abstract; page 680, column 1, lines 1-3; column 2, "Administration of Viral Oncolysate"; Cassel et al., page 857, column 1, "Viral Oncolysate: Preparation, Dosage"; Bohle et al., "Postoperative Active Specific Immunization in Colorectal Cancer Patients with Virus-Modified Autologous Tumor-Cell Vaccine", page 1517; "Vaccine", page 1518.

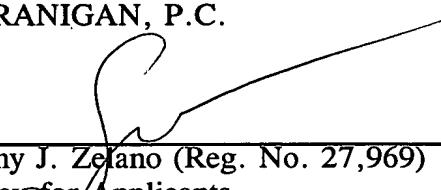
According to the aforementioned references, the purpose of administering the vaccine or oncolysate is to stimulate the patient's immune response to cancer. In addition to the absence of any teaching that the virus, alone, is cytotoxic or cytopathic to the cancer, the amounts of virus employed in such prior art is actually ineffective in achieving such effect when administered, alone, to a mammal. See, Lorence declaration, Paragraph No.

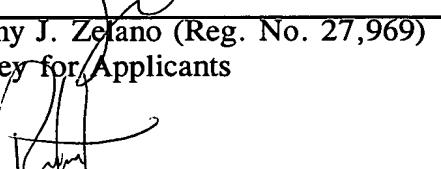
4. According to calculations performed by Dr. Lorence, the amounts of virus employed by Cassel et al. were  $2.7 \times 10^4$  PFU/kg; Murray et al.,  $2.2 \times 10^4$  PFU/kg; and Bohle et al.,  $1.1 \times 10^5$  PFU/kg. Experiments performed by Dr. Lorence or on his behalf demonstrated that such doses are ineffective for treating cancer when administered systemically. The calculations and experiment are worst case scenarios; e.g., Bohle et al. resuspended the cells after incubation with the virus, suggesting that its concentration could be much lower than the calculations discussed herein. There is no indication or suggestion in Murray et al., Cassel et al., or Bohle et al. that the Newcastle disease virus is administered to the patient in an amount which alone is cytotoxic or alone is cytolytic to tumor cells within the patient, and especially not as the sole anticancer effective agent. Moreover, they do not disclose administration of a mesogenic strain nor of one substantially free of red blood cells, e.g., exposed to low speed centrifugation. Thus, the references fail to teach all material aspects of any claims and therefore can not anticipate them; this is especially true of the claims reciting even further distinguishing characteristics.

In view of the comments, withdrawal of the rejections is respectfully requested.

Respectfully submitted,

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